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ABSTRACTS

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Prognosis of renal function after kidney biopsy in renal transplantation. *M. Zeiler, M.J. Mihatsch, and G. Thiel, Kantonsspital Basel, Institut für Pathologie und Abteilung für Nephrologie, Basel, Switzerland.* Rejection is the most limiting factor in long-term kidney transplant outcome despite optimal clinical treatment. Clinical parameters in correlation with histological features were evaluated retrospectively. Exclusively initial allograft biopsies were considered. Biopsy timepoint after transplantation (Bx-time, in days) was noted. The following histological categories were analyzed: (a) vascular rejection (VR); (b) glomerulonephritis (GN); (c) aggressive interstitial-cellular rejection (ICR); and (d) acute tubular necrosis (ATN). Other morphologic features were not evaluated. Plasma creatinine levels at time of biopsy (Bx-crea, in μmol/liter) were correlated with those 12 months post-biopsy. Endpoints were the absolute (Δ-crea) and percent (%-crea) change of plasma creatinine and the return to dialysis.

	VR (N = 171)	GN (N = 45)	ICR (N = 70)	ATN (N = 25)
Bx-time	243 ± 43, 34	494 ± 68, 429	107 ± 23, 36	46 ± 25, 13
Bx-crea	407 ± 26, 238	213 ± 28, 162	216 ± 15, 189	714 ± 71, 999
%-crea	−12 ± 6, −16	−3 ± 5, −2	−10 ± 5, 16	−65 ± 7, −84
Δ-crea	−106 ± 30, −24	−35 ± 24, −4	−34 ± 11, −27	−576 ± 80, −829
Dialysis	44% (N = 75)	13% (N = 6)	10% (N = 7)	12% (N = 3)

Mean ± SEM, median.

In the group of patients showing VR Bx-crea was significantly higher in patients on dialysis after one year (571 ± 41 μmol/liter) than in those with a functioning graft (279 ± 27 μmol/liter). Return to dialysis was significantly more frequent in patients presenting VR than in any other group. In conclusion, early biopsy is recommended in every case of renal function deterioration in order to prevent extensive, therapeutically irresponsive tissue damage.

Effect of salt and water diuresis on urine endothelin-1 in humans. *M. Zeiler, B.-M. Löffler, H.A. Bock, and G. Thiel, Kantonsspital Basel, Abteilung für Nephrologie, F. Hoffmann-La Roche, Basel, Switzerland.* Differences in urine endothelin-1 excretion (uET-1/min) depending on the type of urine flow stimulation were reported in humans. Cell culture studies have shown an osmolality dependent ET-1 production. We therefore investigated uET-1/min in different states of urine osmolality provoked by glucose (water diuresis) or NaCl (salt diuresis) infusion. In six healthy subjects uET-1/min was measured during overnight urine collection and during water diuresis stimulated by glucose 5% infusion (15 ml/kg for 90 minutes). NaCl 0.9% infusion (20 ml/kg for 90 minutes) was given on a separate day to provoke salt diuresis. For each type of infusion six measurements were achieved before and 12 during infusion. uET-1/min correlated significantly with urine flow in both states of diuresis ($P < 0.01$). No difference in the slope of the two regression lines was found. uET-1/min was higher in states of low urine osmolality. The urine flow dependence of uET-1/min is not altered by water or salt diuresis.

Blunted renovascular response to subpressor angiotensin II after chronic ACE-inhibition in normotensives at risk for hypertension. *H. Schächinger, B. Martina, T. Dieterle, C. Haberthür, P. Huber, A. Bock, R. Ritz, and K. Gyr, Medizinische Universitäts-Poliklinik, DIM, Universitätskliniken, Basel, Switzerland.* Patients with primary arterial hypertension have been found to show blunted angiotensin II (A2) responsivity of the renal vasculature during high salt intake (non-modulators). We hypothesized that pharmacological suppression of A2 formation would reveal similar results in normotensive offspring of hypertensives. Therefore, RBF (C-PAH) was assessed in 33 healthy men [16 with positive family history (FH+) for hypertension (BP: 120 ± 7/66 ± 6 mm Hg, age: 25 ± 3 years) and 17 matched control subjects without family history (FH−) for hypertension (BP: 118 ± 8/61 ± 5 mm Hg, age: 25 ± 5 years.)] during baseline (BL), acute intravenous application of enalaprilat (acute ACEI) and constant infusion of subpressor A2 (1 ng/kg/min) before and after chronic ACE-inhibition (cACEI) by 1 week oral enalapril (30 mg daily).

RBF *ml/min*	FH+ before	FH+ after cACEI	FH− before	FH− after cACEI
BL	926 ± 46	932 ± 59	904 ± 68	1012 ± 67
Acute ACEI	1219 ± 85	1221 ± 81	1102 ± 83	1290 ± 92
A2 infusion	794 ± 29	855 ± 46	801 ± 52	796 ± 43

Renovascular responsiveness to A2 (defined as the RBF decrement from acute ACEI to A2 infusion) increased in FH− (before chronic ACEI: 301 ± 75, after: 494 ± 79 ml/min) but failed to increase in FH+ (before chronic ACEI: 425 ± 89, after: 366 ± 74 ml/min) ($P < 0.01$). After pharmacological suppression of A2 generation, normotensives at risk for hypertension show a blunted A2 responsivity of the renal vasculature. The presented data are thus consistent with a hereditary, 'non-modulating,' chronically stimulated renal A2 system in primary arterial hypertension.

Erythropoietin resistance. *A. Colombi, S. Rüegger, and E. Grüter, Kantonsspital, Luzern, Switzerland.* Patients (PAT) on renal replacement therapy require different doses of recombinant human erythropoietin (EPO) to maintain hematocrit (HK) levels in the range of 0.30 to 0.35. EPO resistance has been suggested when high doses of EPO are needed. **Aim of our study:** To analyze the EPO dose required in 29 PAT on chronic hemodialysis (HD) and 26 PAT on continuous peritoneal dialysis (PD) to keep HK in the above range and to investigate clinical signs and laboratory markers for conditions known to cause EPO resistance. PAT with polycystic kidney diseases were excluded. **Results:** EPO dose in HD-PAT 5.448 ± 3.979 U/week, in PD PAT 1.885 ± 2.044 U/w ($P < 0.001$). In HD PAT there is no significant correlation between EPO requirement and serum ferritin levels, CRP, reticulocyte count, and intact PTH. EPO dose also does not correlate with parameters of hemolysis (LDH). Furthermore, EPO dose was not affected by angiotensin converting enzyme inhibitor, but aluminum-containing phosphate binders enhanced the required EPO dose ($P = 0.05$). PAT with EPO doses <6.000 U/w required increasing doses with increasing Kt/V; those with doses >6000 U/w in

contrast required lower doses with increasing Kt/V. Extraordinarily high EPO doses (14.188 ± 8.626 U/w) were required in 16 HD PAT with failed kidney grafts *in situ*, while 9 PAT who had nephrectomy after graft failure required significantly less EPO (3.666 ± 2.108 U/w, $P < 0.001$). PAT on PD maintained HK with the lowest dose of EPO even after graft failure. After graft nephrectomy one diabetic patient still needed high EPO dose with a functioning pancreatic graft. **Conclusions:** (1) PAT on PD require less EPO than PAT on HD to maintain HK of 0.30–0.35. (2) Up to a cut-off level of 6.000 U/w we found a direct and above this level an inverse correlation between the EPO dose and Kt/V. (3) Kidney grafts without significant function increased EPO requirement in PAT returning to HD. (4) The induction of EPO resistance is probably not specific for renal grafts and may also result after transplantation of other organs. The mediator causing this resistance is not yet known.

Risk factors for chronic renal allograft rejection. *V.R. Broger Ribi, and U. Binswanger, Nephrologie, Universitätsspital, Zürich, Switzerland.* Out of 266 recipients of renal allografts transplanted from 1988–1991, 34 were diagnosed as suffering from chronic rejection by the observation of slowly rising serum creatinine concentration, development of hypertension and proteinuria. Occasionally, the diagnosis was directly proven by biopsy. For comparison, 34 age- and sex-matched controls with normal transplant function were selected. Data evaluated were as follows:

	Patients	Controls
HLA mismatches	4.6 ± 1	4.5 ± 1
Mean antibody titer %, maximum/actual	16/5	16/7
Immediate function	29/34	29/34
Rejection <90 days, patients	20/34	13/34
Total	28	14[a]
Severe	7	1[a]
>90 days	9/34	1/34[a]
Risk for primary CMV	6/34	1/34[a]
CMV disease	4/34	0/34[a]
Immunosuppression		
Prednisone withdrawal	6/34	20/34[a]
Cyclosporine mg/kg/day	3.3 ± 0.9	3.2 ± 0.9
Serum trough level	130 ± 42	136 ± 47
Azathioprine mg/kg/day	0.8 ± 0.4	0.8 ± 0
At 3 years post-transplant		
Cholesterol mmol/liter	5.7 ± 1.3	5.6 ± 1.2
Triglyceride mmol/liter	2.2 ± 2.3	1.8 ± 1.2
Uric acid μmol/liter	520 ± 123	453 ± 107

[a] patients vs. controls, $P < 0.05$.

In conclusion, 2 or more severe early rejections, unsuccessful steroid withdrawal, CMV infection and disease, and higher uric acid concentration are more frequently observed in chronic rejecting allograft recipients than in controls.

Islet cell transplantation in IFNγ receptor deficient mice. Are Th2 cells upregulated? *J. Steiger, P. Nickerson, B. Ryffel, M. Hermle, D. Roubaty, M. Heim, and G. Thiel, University of Basel, Basel, Switzerland and University of Manitoba, Manitoba, Canada.* IFNγ (Th1 cytokine) is strongly associated with rejection, down-regulates Th2 cells, is responsible for DTH and the up-regulation of MHC class II. We therefore wanted to test the following hypotheses: (a) signaling through the IFNγ receptor (IFNγR) is relevant for rejection; and (b) in the absence of IFNγ signals Th2 cells would dominate the immune response. We transplanted islets from DBA/2J donors (H-2^d) under the renal capsule of IFNγR knock-out (KO) mice (H-2^b) and wild type (WT) controls. Recipient mice were rendered diabetic one week prior to transplantation and graft function was determined by measuring blood glucose levels. All IFNγR KO mice rejected their islet allograft without any delay as compared to WT controls. Sequential histological examination on days 4, 6, 9 and 12 post-transplant showed a cytodestructive mononuclear cell infiltrate of the islets in both groups. To test whether rejection is mediated by T-cells in IFNγR KO mice, we treated the allograft recipients with anti-CD3 (25 μg/day), which is known to delay allograft rejection by neutralizing the T-cells. Under this treatment none of the treated IFNγR KO mice rejected the allograft. Intragraft cytokine gene transcripts from IFNγR KO mice and WT control were analyzed by competitive template reverse transcriptase assisted polymerase chain reaction on days 4, 6, 8 and 14 post-transplant. IL-2, IL-4, IL-10, IFNγ, granzyme B and TCRcβ gene transcripts were up-regulated after transplantation and peak around day 8 in WT and IFNγR KO mice. Interestingly, all gene transcripts, with the notable exception of IL-4, are diminished at any given day in IFNγR KO mice compared to the WT control. Regarding the Th1/Th2 paradigm it was striking that, although IL-4 seems to be more highly expressed in this IFNγ deficient system, IL-10 was markedly decreased. We conclude that rejection in an IFNγ deficient system occurs at the same tempo as in the WT control and is T-cell mediated. Clearly, IFNγ receptor signaling is not required for allograft destruction. Although IFNγR signaling is absent and IL-4 is expressed, IL-10 gene transcripts are markedly diminished. Thus, polarized expression of TH2 cells was not evident. We hypothesize that rejection in these mice is mediated by an IL-2 producing Th0 like cell.

Tolerance induction by blocking costimulation: Is it important for the T-cell to encounter the antigen? *J. Steiger, P. Nickerson, W. Steurer, A. Steele, M. Hermle, D. Roubaty, G. Thiel, and T.B. Strom. University of Basel, Switzerland, University of Manitoba, Manitoba, Canada, and Harvard Medical School, Boston, Massachusetts, USA.* Classical allograft rejection is a T-cell mediated process. Two signals are required to activate T-cells. Signal 1 is provided by the T-cell receptor and signal 2 (or costimulation) by the interaction of CD28/CTLA4 on the T-cell to B7 on the antigen presenting cell (APC). Blocking signal 2 during T-cell activation leads to anergy *in vitro* and tolerance *in vivo*. Therefore, blocking costimulation is a very attractive target for immunomodulation. We constructed two murine CTLA4 fusion proteins. In both forms we coupled the extramembranous part of CTLA4 to the Fcγ2a part of the IgG2a. In one construct we mutated the high affinity FcγRI receptor binding site and the C'1q binding site. This results in 2 CTLA4/Fc fusion proteins: one with (L) and the other without (NL) antibody dependent cellular cytotoxicity (ADCC) and complement directed cytolysis (CDC) activity. The hypothesis is that NL CTLA4/Fc binds to B7 but does not target APCs for ADCC or CDC. The protein coats B7+ cells and thereby inhibits costimulation. Thus, we hypothesized that NL CTLA4/Fc is more effective in achieving allograft tolerance, then L CTLA4/Fc. We transplanted islets from DBA/2J or Balb/c donors (H-2^d) under the renal capsule of B6AF1 mice (H-2^b). Recipient mice were rendered diabetic one week prior to transplantation and graft function was determined by measuring blood glucose levels. To induce permanent engraftement we used 4 protocols: (1) NL; (2) L CTLA4/Fc 100 μg from day (−1)–14; (3) NL; or (4) L CTLA4/Fc 500 μg on day 2 as a single dose. Using DBA/2J donors, the incidence of tolerance is low (15–40%). There is no difference in allograft survival, if CTLA4/Fc is given for 14 days or as a single dose, but interesting to note is that NL CTLA4/Fc is more potent in inducing long-term engraftement when compared to the L form ($P < 0.02$). Using Balb/c donors, permanent engraftment is achieved in 85% (NL). Again the NL form results in a higher number of long-term engraftement ($P < 0.001$). We conclude that NL CTLA4/Fc is more potent in inducing permanent engraftment. Targeting APC's for lysis might not be a good concept for tolerance induction because T-cells must encounter the antigen. No difference is seen when the protein is given on day 2 or for 14 days.

Urologic complications after two different techniques of ureteric anastomosis for renal transplantation with the use of prophylactic ureteric stents. *M. Bianchetti, N. Frischmuth, T. Gasser, P. Vogelbach, and G. Thiel, Department of Innere Medizin und Chirurgie, Kantonsspital und Universität Basel, Basel, Switzerland.* Urologic complications after renal transplantation remain a major problem. Therefore, we compared two different types of ureteric anastomosis techniques in renal transplant recipients. Each technique was used over a period of one year. In June 1995 we switched from the direct spatulated pull-through ureteric anastomic technique (Modified Leadbetter-Politano, MLP) to an external ureteroneocystostomy (UNC) technique. All of the 65 patients (39 male, 26 female) with the MLP technique received a ureteric stent. These percutaneous ureteric stents were usually removed 9–15 (mean 12.7) days post-transplant. All of the 54 UNC patients (37 male, 17 female) received a double-J stent, which was removed cystoscopically between 15 to 55 (mean 22.4) days after renal

transplantation. The median age was 46.5 years in the MLP group and 46.4 years in UNC recipients. The MLP patients showed an overall urologic complication rate of 27.7% (obstruction 10.7%, leakage 3.1%, clot retention 4.6%, vessel/ureteral angulation 3.1%, bleeding 2%, stent problems 3.1%, allograft pyelonephritis 0%) versus 18.5% in the UNC group (obstruction 11.1%, leakage 1.8%, clot retention 1.8%, vessel/ureteral angulation 1.8%, stent problems 0%, allograft pyelonephritis 1.8%). This difference of overall complications between the two groups did not reach statistical significance (chi-square test), but the odds ratio of 1.69 points to a lower risk of complications in the UNC group. One patient in the MLP group died due to ureter obstruction and leakage. No other allograft was lost because of urological complications. Based on the slightly lower complication rate we decided to continue the external UNC technique to reconstruct the urinary tract in renal transplantation.

Follow-up of polycystic kidney disease patients in a chronic hemodialysis center. *D. Teta, A. Movaffaghi, F. Steinhauslin, G. Vogel, and J.P. Wauters, Division de Néphrologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.* Clinical manifestations of autosomal dominant polycystic kidney disease (ADPKD) during chronic hemodialysis (HD) seem to differ from those of patients with other causes of renal failure. In this retrospective study, we have compared their morbidity, mortality and vascular access obstructions with a matched control (C) group. From 1974 to 1994, 717 patients were enrolled in our HD program. Among 56 ADPKD patients, 48 (25 men, 23 women) could be analyzed and compared to 48 (25 men, 23 women) of the C group. Mean age at start of HD was 52 years (22–76) and 53 (25–76), respectively, while mean follow-up (beginning of HD until death or transfer to another modality) was 57 months (1–229) and 71 months (1–234). Eighty-eight % of the ADPKD group and 92% of the C group suffered from arterial hypertension at some time during the follow-up period. Fifty episodes of gross hematuria (important enough to prescribe rest) in 22 patients and 8 cyst infections in 6 patients were observed in the ADPKD group while these complications were absent in the C group. In contrast, the incidence of acute pyelonephritis and lower urinary tract infections was not significantly different (respectively 4 episodes of acute pyelonephritis in 4 patients of the ADPKD group vs. 15 in 4 of the C group and 26 episodes of lower urinary tract infection in 15 patients vs. 22 in 13). Of 30 patients with hepatic cysts, only 3 presented cyst hemorrhages, one cyst infection and 2 cyst ruptures. Eight strokes in each group were identified of which 2 were hemorrhagic in the C group only. Ischemic heart disease was recorded in 12 patients with ADPKD and 20 in the C group. A.V. fistula obstructions were registered 79 times in 26 patients with ADPKD and 42 in 17 control cases (0.35 vs. 0.15 episode/year/patient). Twenty-two patients of the ADPKD and 30 of the C group died. We conclude that in this single center retrospective survey, ADPKD patients frequently present specific complications during their HD period but cerebral and cardiovascular morbidity is similar to controls; the incidence of vascular access thrombosis is clearly higher, possibly related to higher hematocrit and vascular reactivity.

Evaluating solute excretion in the neonate: Is the solute to creatinine ratio in urine samples a good index? *V. Matos and J.-P. Guignard, Département de Pédiatrie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.* Creatinine (Cr) excretion rate being relatively constant in a given subject, the solute to Cr concentration ratio in single voided urine samples yields a satisfactory standardization of solute excretion in children and adults. To define whether this method was also valid in the neonate (NN), we studied 48 healthy term NN (2 to 7 days old; median age 2 days) and 168 healthy children (age 1 month to 2 years). The urinary Cr concentrations and osmolalities (osm) were determined from 2 morning random urine samples collected 2–4 (neonates) and 7 days (children) apart. In the NN, Cr concentration in the first urine sample was significantly higher than in the second urine sample ($P < 0.05$); this difference was not significant in the children's group. When the two groups were compared, the Cr concentration was highly scattered and elevated in the NN ($P < 0.01$). Even after correction for urine dilution (by using the Cr to osm ratio), the levels of Cr remained elevated (see table):

Age *months*	U_{Cr} *range* *μmol/liter*	U_{Cr} (median) *μmol/liter*	U_{Cr}/osm *median* *μmol/liter*
0.1	680–19300	7060	19.6
1–6	263–8550	1107	6.8
6–12	285–5807	1710	4.9
12–24	516–9970	2250	4.8

The high levels of urinary Cr and the important scatter of values observed in the first days of life demonstrate that factors other than the lean body mass and glomerular filtration rate (GFR) determine the creatinine excretion rate. Clinical observations have shown that the NN inherits a variable amount of creatinine from its mother, which will be cleared during the first days of life. In addition, experimental evidence indicates that the immature renal tubule is permeable to Cr, allowing back-diffusion from the tubule to the blood. These two factors, as well as the rapid maturation of the GFR in the first two weeks of life, probably determine the high levels of urinary Cr and the important scatter in its excretion observed in the NN. We conclude that the urinary creatinine concentration cannot be used to standardize solute excretion in a single urine sample in the neonate.

Different solute transport profile in pre- and postdilution hemodiafiltration with on-line production of bicarbonate infusate. *D. Kiss, M. Löffel, and J. Muser, Abteilung für Nephrologie, Med. Klinik, Kantonsspital Liestal, Liestal, Switzerland.* High-flux hemodiafiltration (HDF) presently offers the most efficient extracorporal treatment modality in patients with end-stage renal disease. On-line production of substitution fluid by cold sterilization of dialysate permits virtually unlimited fluid volume exchange. To find out the changes in solute transport along the molecular clearance range during on-line pre- and postdilution HDF with different quantities of infusate, we performed clearance (CL) studies in 14 chronic hemodialysis patients. In predilution HDF the infusate amounted from 0–80 liters and in postdilution HDF from 0–20 liters. The reduction rate of urea (MW = 0.06 kDa, of beta-2-microglobulin (MG/MW = 11 kDa) and cystatin (CY/MW = 13 kDa) were determined. We used a Gambro AK-100 ultra-pure dialysis machine for HD and on-line HDF and a high-flux dialyzer (Polyflux 21). The treatment time was 240 minutes, the blood flow rate was set at 400 ml/min and the dialysate flow rate was 700 ml/min. The RR was calculated from the pre- and post-treatment value, adjusted to the patients weight and intradialytic weight loss. Results are expressed as mean ($N = 13$) and are given in %. Statistical analysis was performed with the paired *t*-test.

	HD	Pre-HDF			Post-HDF	
Infusate *liters*	0	20	40	80	10	20
Urea-RR %	75	71	70	68	70	75
MG-RR %	58	61	67	74[a]	61	80[a]
CY-RR %	60	63	72[a]	71[a]	66	72[a]

[a] $P < 0.05$.

As a biochemically stable protease inhibitor, CY is proven to be superior to beta-2-MG as a biochemical marker for determining the rates of middle molecular removal. In postdilution HDF there is no change in the LM-RR, but there is a significant increase (+22%) of the MM-RR only with 20 liters of infusate. In predilution HDF there is a decrease of the LM-RR and a significant increase of the MM-RR. The maximal increase (+16%) is achieved with 40 liters of infusate. The proven efficiency of high-flux dialyzers with large surface area for dialysis means that the benefits of HDF are comparatively slight.

Attenuation of anti-Thy1.1 Nephritis by inhibition of matrix metalloproteinases. *K. Steinmann-Niggli and H.P. Marti, Abteilung für Nephrologie, Inselspital Bern, Bern, Switzerland.* Anti-Thy1.1 nephritis represents a well-characterized animal model of immune complex-mediated, mesangial proliferative glomerulonephritis. After induction of anti-Thy1.1 nephritis in rats, mesangiolysis is followed by an increase in proliferation of

mesangial cells (MC) with augmented expression of matrix metalloproteinase-2 (MMP-2) and by an accumulation of extracellular matrix (ECM); marked proteinuria occurs during the first days of the disease. The aim of the present study was to determine the effect of the synthetic MMP inhibitor, BB-1101, on the development of the nephritis. Four groups of male Wistar rats were studied: healthy rats ($N = 9$), treated healthy rats ($N = 18$), nephritic rats ($N = 18$), and treated nephritic rats ($N = 18$). The 63 animals were kept in metabolic cages. Anti-Thy1.1 nephritis was induced by intravenous injection of OX-7 IgG (1 mg/kg body wt). The therapy consisted of intraperitoneal applications of BB-1101 (30 mg/kg body wt/day), initiated 2 days prior to induction of nephritis. Treatment of nephritic rats with BB-1101 resulted in a significant decrease of proteinuria: the median area under the curve of protein/creatinine ratios versus time, considering 24 hour urine specimen during days 0–6, was 0.97 g/mM, compared to 2.00 g/mM in the untreated nephritic group. Non-nephritic rats displayed negligible proteinuria. Renal histology was analyzed 11 days after induction of nephritis. Total cell count of glomerular cross-sections ($N = 63$/group) in BB-1101 exposed nephritic rats was significantly less than in the untreated nephritic group (66 ± 8 versus 85 ± 12). Both groups of healthy animals displayed cell counts in the order of 55 ± 10. The increased size of the glomeruli in nephritic rats was reduced to almost normal by the MMP inhibitor. Accumulation of ECM in nephritic rats was also ameliorated by BB-1101. Therefore, therapy of nephritic rats with BB-1101 demonstrated beneficial effects in four parameters, which are characteristic for the disease model. In conclusion, MMP inhibition may represent a new approach to the treatment of mesangial cell-mediated forms of glomerulonephritis.

TNFα and IL-1β enhance 11β-hydroxysteroid dehydrogenase reductase activity in rat mesangial cells. *G. Escher, B.S. Vishwanath, B.M. Frey, and F.J. Frey, Abteilung für Nephrologie, Inselspital Bern, Bern, Switzerland.* Intracellular access of steroids to gluco- and mineralocorticoid receptors is regulated by 11β-OHSD1 and 11β-OHSD2 which interconvert active 11β-OH- and inactive 11-keto-steroids. The purpose of the present study was to establish whether: (i) GMC express 11β-OHSD; (ii) 11β-OHSD, if present, is relevant for the glucocorticoid effect in GMC; and (iii) GMC stimulatory cytokines modulate 11β-OHSD. RT-PCR analysis revealed a significant 11β-OHSD1 and a negligible 11β-OHSD2 expression. Differential measurements of the activities of 11β-OHSD isoenzymes in GMC cultures and GMC extracts and analysis of Western blots demonstrated the presence of 11β-OHSD1. In order to establish whether 11β-OHSD1 modulates glucocorticoid effects in GMC, the inhibitory effect of corticosterone on IL-1β stimulated group II phospholipase A2 (PLA2) was analyzed. The potency of corticosterone to reduce transcription and activity of PLA2 was increased by the addition of an inhibitor of 11β-OHSD1. This effect of corticosterone was mediated by glucocorticoid receptors as shown by experiments with RU 486. Stimulation of GMC with IL-1β and TNFα, but not IL-3, IL-6, PDGF or PMA, resulted in a dose-dependent increase in expression of 11β-OHSD1, with a more than 5-fold increase in its reductase but not oxidase activity. This effect is specific, since IL-1β and TNFα did not affect the reductase or oxidase activity of the 17β-OH-steroid dehydrogenase. **Conclusion:** GMC express significant amounts of 11β-OHSD1, which modulate the anti-inflammatory effect of 11β-OH-steroids. IL-1β and TNFα up-regulate specifically the reductase activity of 11β-OHSD1 and by that mechanism counterbalance their own stimulatory effect of cells in the presence of endogenous or exogenous 11β-OH-steroids.

Altered vasopressin (AVP) release and thirst sensitivity in male recurrent renal stone formers with low urine volumes (LVSF). *B. Hess, L. Zipperle, R. Takkinen, K. Farina, and Ph. Jaeger, Med. Universitätspoliklinik, Inselspital Bern, Bern, Switzerland.* Low urine volume (LV) is a common risk factor for recurrent nephrolithiasis. We studied 9 male LVSF (urine volumes < 1200 ml/day on 2 or 3 occasions), aged 46.8 ± 3.4 years and compared them with 9 healthy male controls (C), aged 45.1 ± 3.2 years. After they fasted and abstained from tobacco, alcohol and caffeine overnight, subjects were infused 5% saline at 0.06 ml/min/kg for 120 minutes. At intervals of 15 minutes (including 15 and 75 min after the infusion was stopped), subjects rated their thirst on an uncalibrated visual analog scale (10 cm), and blood was drawn for measuring plasma osmolality (OSMO) and AVP (RIA, Nichols). Thresholds and sensitivities for thirst and AVP release were obtained from the x-intercepts and slopes of linear regression lines derived from correlations of thirst and AVP, respectively, with OSMO. All values are means ± SE. Thresholds (293.7 ± 2.1 vs. 294.1 ± 2.7 mOsm/kg) for AVP release were equal in LVSF and C, respectively, and AVP levels were similar in LVSF and C during saline infusion. After cessation of saline infusion (between 15 and 75 min), total amount of AVP secreted over baseline (area under the curve) was higher in LVSF than in C (248.3 ± 33.5 vs. 79.3 ± 25.0 pg/ml, $P = 0.047$). Whereas thirst thresholds did not differ between LVSF and C (295.8 ± 2.3 vs. 292.5 ± 1.0 mOsm/kg), individual thirst sensitivities were lower in LVSF (2.88 ± 0.30 vs. 4.18 ± 0.42 in C, $P = 0.047$). On respective plots of pooled values of AVP and thirst ratings against OSMO, the slope of increase in thirst with rising OSMO was significantly lower ($P < 0.0001$) in LVSF ($r = 0.51$, slope 1.92, $P = 0.0001$) than in C ($r = 0.79$, slope 3.54, $P = 0.0001$). Whereas AVP levels were not correlated with rising OSMO in C, a significant positive correlation was obtained in LVSF ($r = 0.57$, slope 0.17, $P = 0.0001$). In conclusion, when challenged by a defined osmotic stimulus (5% saline), LVSF exhibit reduced thirst sensitivity and increasing AVP levels with rising OSMO, and elevated AVP secretion persists after cessation of the osmotic stimulus. These abnormalities appear to contribute to LV as a risk factor for recurrent renal stone formation.

Routine biopsy of renal grafts: A high prevalence of cyclosporine-associated arteriolopathy. *G. Ashuntantang, R.E. Lemoine, C. Stoermann-Chopard, J.-F. Bolle, P. Morel, and M. Leski, Division de Néphrologie du Département de Médecine; Département de Pathologie, et Unité de Transplantation du Département de Chirurgie, Hôpital Cantonal Universitaire de Genève, Genève, Switzerland.* Since November 1994, with the availability of automatic biopsy needles, biopsy of renal grafts has become a routine practice in our center. The aim is to identify asymptomatic and reversible lesions at an early age. The histological diagnosis is done using the Banff working classification of kidney transplant pathology. So far, a total of 50 biopsies have been carried out in 50 patients with stable renal function with a mean age of 51 ± 9.6 years. There were 33 males and 17 females. The mean graft age was 5.96 ± 2.7 years, with a range of 2 to 19 years. Mean plasma creatinine levels were 124.9 ± 19 μmol/liters in the six months preceding biopsy, and 127.7 ± 21 μmol/liter at the time of biopsy. The mean dose of cyclosporine A (CsA) used was 4.03 ± 1.3 mg/kg/day; 3.15 ± 0.95 mg/kg/day; 2.72 ± 0.9 mg/kg/day and 2.61 mg/kg/day in the first 3 months, the 6th month, the 12th month post transplantation, and the 3 months preceeding the biopsy respectively. Whole blood CsA trough levels were 331 ± 61.7 μg/liter ($N = 26$), 257.7 ± 77 μg/liter ($N = 25$); and 183.4 ± 73 μg/liter ($N = 14$) in the first three months, the 6th month and the 12th month post-transplantation, respectively. These were polyclonal assays. In patients who had monoclonal assays, the CsA trough levels were 135.4 ± 18 μg/liter ($N = 21$), 129.9 ± 36 μg ($N = 22$), and 121.6 ± 32 μg/liter ($N = 34$) in the first 3 months, the 6th month, and the 12th month, respectively. The mean CsA trough levels using the monoclonal assay (the only assay done in our center now), was 111.3 ± 21 μg/liter in the 3 month period preceding the biopsy in all 48 of the 50 patients on CsA therapy. We found CsA arteriolopathy in 38 of the 50 grafts, 21 scored as grade I, 13 as grade II, and 4 as grade III. Among the 29 grafts of more than 5 years of age, 23 had CsA-associated arteriolopathy, with 17 showing interstitial fibrosis. Two of the 6 grafts without arteriolopathy also showed interstitial fibrosis. A striking finding was that of CsA-associated arteriolopathy and striped fibrosis in a patient who had never received CsA. We found no correlation between CsA dose, CsA trough levels, graft age and the occurrence or degree of arteriolopathy. Furthermore, serum creatinine levels were not predictive of histologic lesions. In conclusion, CsA-associated arteriolopathy is a frequent finding in CsA treated patients, irrespective of dose and trough levels, especially given the fact that our CsA doses are on the low side when compared to those reported in the literature. There is no correlation between these lesions and contemporary renal function even in grafts of more than 5 years of age. We therefore question the prognostic significance of these lesions and the rationale for lowering CsA doses when the latter are present. The specificity of these lesions also becomes doubtful.

Renal hemodynamic effects of Bosentan, an endothelin antagonist, and interaction with cyclosporine A: A placebo controlled double-blind study. *I. Binet, A. Wallnöfer, R. Jones, and G. Thiel, Nephrologie Kantonsspital Basel, and Hoffmann-La Roche, Basel, Switzerland.* **Introduction:** Endothelin may play an important role in the cyclosporine A (CsA) induced renal toxicity; therefore, we studied the effects of a non-selective ET-A

and ET-B endothelin antagonist, bosentan (Bo), on the renal hemodynamics, given alone and in combination with CsA. **Methodology:** A double-blind randomized placebo-controlled crossover study was performed in 7 healthy volunteers. Each received Bo 2 × 500 mg/day or placebo, and a dose-adjusted regimen of Sandimmun Neoral® twice daily to achieve CsA target trough levels of 200–250 ng/ml. A renal hemodynamic study was performed on day 1 after a single dose of Bo or placebo alone and on day 8, after 7 days of regular CsA intake with Bo or placebo. The wash-out period was 14 days. Investigated parameters: blood pressure (BP), inulin clearance (GFR), effective renal plasma flow by PAH clearance (ERPF), sodium and lithium excretion fractions (FeNa, FeLi). **Results:** A single dose of Bo lowered the diastolic BP ($P < 0.05$), but had no effect on the renal hemodynamics. CsA + placebo over 7 days lowered the ERPF with a nadir 4 hours after Sandimmun Neoral® intake. This fall of ERPF, as well as the depth of the nadir, were significantly reduced by CsA + Bo. However, CsA + Bo did not attenuate the fall in GFR and the rise of BP observed with CsA + placebo.

	GFR	ERPF
Baseline	120 ± 19	594 ± 84
Bo single dose	114 ± 20[a]	623 ± 123[a]
CsA + placebo (7 days)	103 ± 20	490 ± 93
CsA + Bo (7 days)	103 ± 8[a]	570 ± 106[b]

Mean values ± SD.
[a] not significant
[b] p = 0.01.

FeNa was significantly lower with CsA + Bo (1.6 ± 0.6) as compared to CsA + placebo (2.3 ± 0.6) ($P < 0.01$). Since FeLi remained unchanged, this sodium retention induced by Bo was not due to an effect on the proximal tubule. **Conclusions:** Renal hemodynamics in healthy volunteers are not affected by a single dose of Bo. Given 7 days in combination with CsA, Bo does not prevent the reduction of GFR caused by CsA, but reduces significantly the CsA-induced fall of ERPF and leads to sodium retention. Assuming that CsA nephrotoxicity is mainly due to renal vasoconstriction, then Bo has the potential to attenuate the renal toxicity induced by CsA.

No evidence for hyperfiltration injury in "size mismatched" adult living donor kidneys. *H.A. Bock, I. Binet, N. Frischmuth, P. Vogelbach, Th. Gasser, and G. Thiel, Division of Nephrology and Organ Transplantation, Kantonsspital Basel, Switzerland.* Since hyperfiltration injury may contribute to chronic renal allograft failure, it has been suggested that relatively small kidneys should not be transplanted into relatively big recipients. To evaluate this hypothesis in the context of living donor kidney transplantation, we studied the 104 adult living donor kidney recipients transplanted between 12/88 and 12/94 at our institution. Donors underwent renal function study (inulin clearance and microalbuminuria) before, 1 week after, and 1 year after nephrectomy/transplantation; recipients were studied at 1 month and 1 year. Eleven donor-recipient pairs were excluded from analysis; causes included graft loss within the first year (2), ongoing rejection at the time of the 1-year study (1) and incomplete clearance data (8). Mean donor GFR before nephrectomy (± SD) was 96 ± 20 ml/min/1.73m^2 body surface area (BSA). A "size mismatch" (MM) was assumed to exist if 50% of the donor GFR, divided by the *recipient's* BSA, was below the 99% confidence limit for 2-kidney GFR (<45 ml/min/1.73 m^2). According to this definition, there were 34 "size MM" and 59 "size matched" kidneys:

	Donor GFR pre-NX *ml/min*	Recipient hyperfiltration *GFR/preNx/2*	GFR at 1 month	GFR at 1 year
"Size MM"	79 ± 2[a]	121 ± 5%[a]	47 ± 2[c]	46 ± 3[b]
No MM	110 ± 2	100 ± 3%	55 ± 2	56 ± 2

Mean ± SEM.
[a] $P < 0.005$, [b] $P < 0.01$, [c] $P < 0.05$ MM vs. no MM.

Despite lower GFR and more hyperfiltration, GFR in "MM" kidneys remained stable, and microalbuminuria at one year (111 ± 40 vs. 127 ± 48 mg/24 hr) as well as the mean number of antihypertensive drugs (1.2 vs. 1.3) did not differ between the two groups. Post-Nx hyperfiltration was even more pronounced in the donors (129 ± 2%), yet caused neither microalbuminuria nor loss of renal function. In conclusion, at one year after transplantation, there is no evidence for "hyperfiltration injury" in size-mismatched adult living donor kidneys. The degree of kidney size mismatch usually found among adults does not require size matching.

Long-term follow-up of hemodialyzed patients with the urea monitor: Improvement of dialysis adequacy but not nutritional parameters. *G. Vogel, D. Teta, and J.P. Wauters, Division de Néphrologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.* Total dose of dialysis expressed as Kt/V and protein catabolic rate (PCR) is presently considered to be major determinants of morbidity and mortality in chronically hemodialyzed patients: a total Kt/V ≥1.2 and normalized PCR (nPCR) ≥ 1.0 are now widely recommended. The urea monitor allows measurement of urea kinetics on-line on the dialysate side and thus provides an easy tool at the bedside. From October 1994 till August 1996, a trimestrial measurement of Kt/V and PCR was done in all our center patients ($N = 111$, 58 men and 53 women). Based on pre- and post-dialysis urea levels, all patients appeared to receive an adequate dialysis. After the first measurement, the patients were stratified into 4 groups according to their total Kt/V (≥ or <1.2) and nPCR (≥ or <1.0). In patients of group A ($N = 23$) with Kt/V ≥1.2 and nPCR ≥1.0, no modifications in dialysis schedule or diet were performed. In group B ($N = 12$) with Kt/V <1.2 and nPCR ≥1.0, dialysis therapy was increased by changing successively blood flow and dialyzer's surface. Patients in group C ($N = 48$) with Kt/V ≥1.2 and nPCR <1.0 were prescribed a liberalized regimen and additional oral nutritional support. In patients of group D ($N = 28$) with Kt/V <1.2 and nPCR <1.0, both intensified dialysis and nutritional supply were introduced. After 18 months of follow-up, Kt/V in group A diminished due to decline in residual renal function over time but remained within the prescribed range. For patients in groups B and D with low Kt/V, modification of the dialysis session was followed by an increased Kt/V. In contrast, modifications of nPCR by dietary manipulations were possible during a six month period only and patient's compliance declined afterwards. Sixteen patients died during the follow-up: 7 were in group D and 4 in group C, while only 2 were in group A. We conclude that: (1) the bedside use of the urea monitor allows tailoring dialysis and nutritional therapy in a repeatable and individualized way; (2) dialysis modifications, even minor, are generally effective; (3) a more aggressive and persuasive approach is needed in order to improve nutritional parameters.

Death with functioning graft—An underrated cause of "chronic renal allograft failure." *St. Schaub, H.A. Bock, and G. Thiel, Abteilung Nephrologie, Kantonsspital Basel, Basel, Switzerland.* Standard survival curves frequently form the basis for speculating about the roles of chronic rejection, drug nephrotoxicity, and other factors considered harmful to renal allografts. These standard procedures, however, fail to consider death with intact graft. We wondered whether considering death with intact graft a "censored" endpoint (similar to the patient being lost to follow-up) would affect the interpretation of the post-transplant course in some typical diagnostic and age groups. We used a cohort of 491 cadaveric renal grafts transplanted at our center since 1981 with CsA-based initial immunosuppression. Graft losses were considered censored, if estimated creatinine clearance at the time of death was ≥10 ml/min. Overall, 108 of 231 graft losses (47%) were due to death with a functioning graft. While standard survival calculations showed extremely poor 10-year graft survival in patients with diabetic and analgesic nephropathy (table), the "death-censored" approach demonstrated that graft survival *per se* in these groups was essentially similar to controls.

	Primary renal disease		
10-year graft survival	Diabetic $N = 43$	Analgesic $N = 94$	other $N = 354$
"Standard"	29%	33%[a]	50%
Death-censored	54%	68%	70%

[a] p < 0.05 vs. "other" renal diseases

In contrast, the "death-censored" method uncovered that younger patients incur a much higher risk of losing their graft than older ones ("death-censored" 10 year rates were 51, 68 and 72% for patients < 35 years, 35–60 years and > 60 years, respectively; $P < 0.005$), which was not at all evident from standard calculations (47, 45 and 32% at 10 years; $P = 0.30$). In conclusion, the assessment of the net immunosuppressive effects of different drug regimens or comparisons among transplant centers with different acceptance policies should be based on death-censored survival.

Cyclosporine A pharmacokinetics—Comparison between the standard and the new microemulsion formula using a population-based approach. *F. Schaedeli, F.J. Frey, H.P. Marti, and D.E. Uehlinger, Departement Innere Medizin, Abteilung für Nephrologie, Universität Bern, Bern, Switzerland.* Steady-state pharmacokinetics of once daily administered cyclosporine A (CsA) were investigated in 60 stable renal transplant recipients before and after conversion from the standard formula (S) to the microemulsion formula Neoral® (N). The aim of the study was to investigate the correlation of 12 hour and 24 hour trough levels with the 24 hour area under the curve [AUC(0–24 hr)] in S and N for an adequate dose adjustment after the conversion, and to develop a reliable method for individual AUC prediction for clinical routine monitoring of N. For each of the two formulae, 7 samples per patient were collected from 50 patients (group A) at random time points within two weeks, and 10 blood samples per patient were collected from 10 patients (group B) at fixed time points within 24 hours. A two-compartment population kinetic model assuming time lagged first order oral absorption was fitted to the data of group A, using nonlinear mixed effects modelling (NONMEM), whereas the pharmacokinetic parameters of group B were estimated by classic model independent methods. The data of group B were used to evaluate the predictive power of the population kinetic model. Results are expressed as mean values (coefficient of variation). Mean S doses of 245 (38%) mg resulted in whole blood CsA levels of 214 (32%) ng/ml after 12 hours and of 108 (21%) ng/ml after 24 hours, whereas with mean N doses of 206 (30%) mg, CsA levels were 212 (28%) ng/ml and 132 (25%) ng/ml after 12 and 24 hours, respectively, as measured by specific fluorescence polarization immunoassay (TDx). Assuming no differences in the elimination between the two oral formulae, the estimated bioavailability of N was 25% higher as compared with S. A strong correlation between 12 hour levels and AUC was observed for N, but not for S; the correlation between 24 hour trough levels and AUC was weak for both formulae. The population model of group A predicted individual AUCs of patients from group B with a median deviation of 15% (4% to 52%) from the measured AUCs for N, and 24% (7% to 140%) for S. Switching the oral CsA application from S to N resulted in 60% higher CsA peak levels leading to adverse events that necessitated a change from a once daily to a twice daily dose regimen in some patients.

Long-term recovery of cortical and trabecular bone mass after renal transplantation is modulated by daily dose of cyclosporine A and resolving hyperparathyroidism. *F.F. Horber, K. Lippuner, and Ph. Jaeger, Klinik Schloss Mammern and Policlinic of Medicine, University of Berne, Berne, Switzerland.* Renal transplant patients (RTP) have high trabecular bone fracture rates, probably due to glucocorticoid-induced osteopenia. Whether resolution of secondary hyperparathyroidism and/or continuous reduction of the daily dose of prednisone (DDP, mg/kg/day) as well as dose of cyclosporine A (CsA) applied modulate the known differential effects on trabecular and cortical bone following renal transplantation (RT) in the long run remains unknown. Therefore, 24 RTP (12 females, 12 males) were investigated at 10 ± 1 158 ± 5, 255 ± 5, 349 ± 5, and 524 ± 9 days after RT using DXA technique (Hologic QDR 1000/W). Trabecular compartment (TC) comprised spine, ribs, and pelvis, whereas cortical compartment (CC) included arms and legs. During the first 5 months after RT, bone area (BA), bone mineral content (BMC) and density (BMD) of TC decreased to 96.9 ± 0.7%, 91.9 ± 1%, and 94.8 ± 0.6%, respectively ($P < 0.001$ vs. baseline). Thereafter BA, BMC, and BMD of TC increased continuously reaching significantly higher values when compared with 5 months (98.5 ± 0.8% for BA, 97.9 ± 1.3% for BMC, and 99.5 ± 0.8% for BMD, respectively) after 1 year. When compared with controls, BA, BMC and BMD of TC and its subregions where still decreased in females but not in male patients 1.5 years after RT. In contrast to TC only BA and BMC, but not BMD, of CC increased continuously after RT reaching 104.2 ± 1.3% and 103.6 ± 1.7% of baseline for BA and BMC, respectively, after completion of study, whereas BMD of CC remained unchanged (99.1 ± 0.9% of baseline after 1.5 years). BA and BMC of CC were still significantly lower than those observed in controls in females, but not in male patients at the end of the study. Lumbar and upper femoral BMD demonstrated similar changes over time as observed for TC. Logarithmic serum concentrations of intact PTH at time of RT were correlated with relative changes, occurring during the 1.5 years of observation in BA, BMC and BMD ($r = 0.42$, $P < 0.04$) of CC, but not of TC. No correlation between cumulative dose of prednisone or DDP and change in bone measurements of all densitometric parameters analyzed were detected between all time points ($r < 0.25$) of CC and CT. In contrast, the decrease in DDP correlated positively with recovery of CC-BA and BMC ($r = 0.45$, $P < 0.02$), but not BMD. Cumulative dose of CsA per kg body weight during the first 5 months did not influence the decrease observed in the TC ($r < 0.3$), whereas in the remainder of study, BMD of TC (but not BA and BMC) correlated positively with cumulative dose of CsA ($r = 0.44$, $P < 0.05$). Moreover, BA and BMC, but not BMD of CC increased ($r < 0.5$, $P < 0.01$) with increasing dose of CsA over the 524 days of study. The present data collectively suggest that not only cortical bone recovers following RT (modulated by PTH at time of RT, change in DDP and cumulative dose of CsA), but also TC (modulated by cumulative dose of CsA) despite ongoing immunosuppressive therapy with prednisone, reaching pretransplantation values in males but not in female patients.

Continuous monitoring of blood volume change steering ultrafiltration during hemodialysis: Patient results. *A. Knoflach, H.D. Polaschegg, and U. Binswanger, Nephrologie, Universitätsspital, Zürich, Switzerland.* Seven chronic stable hemodialysis patients were studied during several treatments using continuous ultrafiltration in order to reach dry weight. Continuous hematocrit recording (Crit line) identified delta hematocrit increase (delta blood volume decrease) associated with hypotension. This delta crash crit level minus 1% was set as the limit for ultrafiltration being automatically switched on and off by means of an adapter connected to a Fresenius 2008 monitor during the "experimental" treatment with ultrafiltration rate at 1200 ml/hr. Results were as follows:

Patient	Men/women *bodyweight*	UF (*ml*) Goal	UF (*ml*) Observed	Dialysis Time, *min*	UF goal reached Time, *min*
1	58.5/m	2050	2050	180	105
2	63.5/w	1900	1910	180	90
3	82.5/w	2250	2260	180	165
4	47/m	1150	1190	180	65
5	84.5/m	3400	3386	205	205
6	45.5/w	1350	1370	150	90
7	38.5/w	2650	2658	180	170
Mean		2107.14	2117.71	179.29	127.14
SD		766.17	751.46	15.92	52.35

Conclusion: Hematocrit guided ultrafiltration control permits high initial volume decrease followed by "isovolemic" dialysis. The procedure does not prolong treatment time. Patient tolerance was excellent without hypotension during treatment.

Is heparin therapy necessary in CAPD peritonitis? *C. Nadig, U. Binswanger, and A. von Felten, Nephrologie, Department of Internal Medicine, Universitätsspital, Zürich, Switzerland.* Heparin therapy in CAPD peritonitis seems well-established; it is costly due to the necessity of hospitalization. There are no clinical studies which show benefits of such treatment. The aim of this study was to investigate if heparin therapy in CAPD peritonitis is necessary. One hundred ninety-four samples of peritoneal dialysates were collected from 17 patients over a period of 24 months. Samples were subdivided into a group without peritonitis (<100 leukocytes/μl), a group with mild peritonitis (100–499 leukocytes/μl) and one with severe peritonitis (≥500 leukocytes/μl). The number of leukocytes per μl dialysate and total protein concentrations were determined. Further, dialysates were analyzed by measuring thrombin-antithrombin III (TAT) complexes (indicator of thrombin formation), D-dimers (indicator of fibrinolysis) and PAI-1 (plasminogen activator inhibitor 1). The protein

concentration rose progressively from no peritonitis to mild and severe inflammation. In parallel, TAT complexes and D-dimers increased and correlated strongly in 179 cases ($r = 0.76$; 62 samples showing peritonitis, 117 samples with no peritonitis). However, in the remaining 15 samples of 3 patients, high PAI-1 levels (>40 ng/ml) and low D-dimers were found. Eleven of the 15 samples showed peritonitis, 4 did not. In the 11 samples with peritonitis, high levels of TAT complexes were measured while D-dimers were found to be very low, pointing to a blocked fibrinolysis. The PAI-1 levels were not related to leukocytes or protein concentrations in the dialysates. According to our findings, the general application of heparin in CAPD peritonitis is not necessary. Rare cases can be found with an imbalance of coagulation and fibrinolysis due to high PAI-1 levels (15 of 194 dialysate samples, 11 of the 15 samples showing peritonitis). These cases—which need heparinization—can be identified by measuring low D-dimers in CAPD dialysate at times of peritonitis.

Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: New cause of growth hormone insensitivity in humans. *M. Brüngger, H.N. Hulter, and R. Krapf, Kantonsspital, St. Gallen, Switzerland.* The effects of metabolic acidosis on growth hormone and IGF-1 are poorly understood. We investigated the effects of chronic metabolic acidosis (induced by administration of NH_4Cl, 4.2 mmol/kg body wt per day) on the growth hormone/IGF-1 endocrine axis in 6 normal male volunteers during metabolic balance conditions. NH_4Cl administration resulted in hyperchloremic metabolic acidosis with plasma bicarbonate decreasing from 25 ± 0.4 to 15.5 ± 0.9 mmol/liter ($P < 0.001$). Metabolic acidosis significantly decreased serum IGF-1 concentration from 45 ± 6 to 33 ± 6 nmol/liter ($P = 0.002$), while serum IGF binding protein 3 concentration was not affected significantly. The growth hormone response to growth hormone releasing factor administration (1 μg per kg body wt, intravenous bolus) was enhanced significantly during acidosis. The IGF-1 response to growth hormone administration (0.1 U kg body wt subcutaneously, every 12 hours for 48 hours) was blunted significantly during acidosis. Apparent endogenous serum half-life and metabolic clearance rates of growth hormone were not altered significantly by acidosis. Metabolic acidosis in humans results in a significant decrease in serum IGF-1 concentration without a demonstrable effect on IGF binding protein 3 and is related to a resistance to the hepatocellular action of growth hormone. The primary defect in the growth hormone/IGF-1 axis occurs via an impaired IGF-1 response to circulating growth hormone with consequent diminution of normal negative feedback inhibition of IGF-1 on growth hormone as evidenced by the exaggerated growth hormone response to growth hormone releasing factor administration.

Impact of dietary advice on urinary supersaturation in male recurrent idiopathic calcium renal stone formers (RCSF). *B. Hess, H. Mauron, R. Michel, D. Ackermann, and Ph. Jaeger, Medizinische Poliklinik und *Urologische Klinik der Universität Bern, Bern, Switzerland.* Low urine volume and high meat protein intake are recognized epidemiological risk factors of calcium nephrolithiasis. By means of EQUIL 2, we calculated relative supersaturations of calcium oxalate (RS_{CaOx}) of 24 hr urines of 68 healthy male controls (C, 1 urine collection) and 40 male RCSF *before* (2 or 3 urines) and *after* (1 urine) dietary advice (DA) had been provided as the only treatment. The main goals of DA were: (1) to keep urine volume (V) above 2000 ml/day; and (2) to reduce meat protein intake to 5 servings/week. Except for $U_{Na} \times V$ which fell from 234 ± 12 to 203 ± 11 mmol/day ($P = 0.003$), no significant changes were noted in urines of RCSF after DA, and RS_{CaOx} was unchanged. However, when dividing RCSF into hypercalciurics (HCSF, $U_{Ca} \times V > 9.00$ mmol/day, $N = 14$) and normocalciurics (NCSF, $N = 26$), reasons for the apparently lacking effects of DA became more evident (24 hr urine excretions, means ± SE):

	HCSF		
DA	V *ml*	$U_{Urea} \times V$ *mmol*	RS_{CaOx}
Before	2366 ± 181	505 ± 23	8.90 ± 1.01
After	2165 ± 222	421 ± 29[a]	8.91 ± 1.01

	NCSF		
DA	V *ml*	$U_{Urea} \times V$ *mmol*	RS_{CaOx}
Before	1793 ± 10	426 ± 32	5.65 ± 0.56
After	2061 ± 123[a]	463 ± 30	6.20 ± 0.60

[a] $P < 0.05$ vs. before DA

Since protein consumption ($U_{Urea} \times V$) was elevated in HCSF, DA mainly aimed at reducing protein intake which indeed was reduced; however, V also tended to fall. In *NCSF*, DA primarily focused on V which actually rose, as did—unintentionally—$U_{Urea} \times V$, $U_{Ox} \times V$, $U_{Ca} \times V$ and thus RS_{CaOx}. When pooling all 24 hr urines from HCSF and NCSF before and after DA ($N = 103$), the single parameter which best predicted RS_{CaOx} was urinary oxalate concentration ($r = 0.816$, $P = 0.0001$). In conclusion, DA may only be successful in reducing RS_{CaOx} if *both* V as well as meat protein intake are addressed in *all* RCSF. In addition, we demonstrate that urinary [Ox] is the most simple clinical index of RS_{CaOx}.

Reduced proteinuria on combined verapamil SR/quinapril instead of nifedipine CR/quinapril in a patient with diabetic nephropathy. *D. von Daeniken, D. Rösler, R. Cacciatore, R. Sieber, and B. Hess, Medizinische Klinik, Zieglerspital, Bern, Switzerland.* Short-acting nifedipine (N), although it efficiently lowers blood pressure (BP), may increase proteinuria (U_{Prot}) in patients with diabetic nephropathy (DN); no data exist on the effects of long-acting forms of N on U_{Prot}. Other calcium channel blockers (CCB), such as the non-dihydropyridines, are able to reduce U_{Prot} in patients with DN, and combined verapamil/ACE inhibitor treatment produces greater reduction in U_{Prot} and better preservation of renal function than either compound alone. A 66-year-old woman with a 19-year history of diabetes mellitus (insulin-dependent) and hypertension with overt nephropathy, polyneuropathy and retinopathy was admitted for treatment of a foot ulcer. Main findings were as follows: 164 cm, 76 kg, massive edema, BP 170/80 mm Hg, heart rate 80/min, glucose 6.9 mmol/liter, HbA1c 8.0%, creatinine 219 μmol/liter, albumin 17 g/liter, CRP 61 mg/liter, Lc 10.1 × 10^9/liter. While still on the previously established combination therapy with nifedipine CR 60 mg/quinapril 2 × 20 mg/day and with BP values of 140–180/60–80 mm Hg, C_{Cr} was 20.9 ml/min./1.73 m^2 and U_{Prot} 9.0 g/24 hr. Whereas all other treatment modalities were unchanged, antihypertensives were switched to verapamil SR 120 mg/quinapril 2 × 20 mg/day. After 1 month, BP remained at 140–160/70–80 mm Hg, C_{Cr} was 16.1 ml/min./1.73 m^2, and U_{Prot} returned to 5.3 g/24 hr. After 2 months, with stable BP values and serum albumin of 24 g/l, C_{Cr} and U_{Prot} were 16.7 ml/min./1.73 m^2 and 3.6 g/24 hr, respectively. The effect was sustained after 7 months, when respective values were 15.0 ml/min/1.73 m^2 and 1.6 g/day. In conclusion, it appears that the antiproteinuric efficacy of combined CCB/ACE inhibitor treatment in DN may be affected by the type of CCB, and we suggest that long-acting nifedipine, despite its BP lowering activity, may have contributed to the massive proteinuria observed in the present case.

Histological features of cellular renal allograft rejection correlated with clinical parameters: An analysis of 111 cases. *V. Nickeleit, E.C. Vamvakas, M. Pascual, J. Poletti, and R.B. Colvin, Massachusetts General Hospital, Boston, Massachusetts, USA; St. Vincent Med. Center, Los Angeles, California, USA; and University of Basel, Basel, Switzerland.* **Background:** The diagnosis of acute cellular rejection (ACR) in renal allograft biopsies (bxs) is based on the presence of a mononuclear cell infiltrate, tubulitis, and endothelialitis (= endarteritis), which is regarded as typical for ACR. However, little is known about the prognostic and therapeutic significance of these histologic features. **Design:** One hundred eleven renal allograft bxs with ACR were analyzed (excluding chronic rejection). The study was limited to early bxs (41 ± 38 days post transplantation; 80 initial bxs) performed for deterioration of graft function. Sixteen histological criteria were scored and correlated with clinical parameters [one year graft survival, 6 month and 12 month serum creatinine levels (Cr), and response to steroid or antibody therapy]. **Results:** Patients without endothelialitis showed a better response to bolus steroid treatment (serum creatinine ≤ 110% of baseline) than those with endothelialitis (total $N = 75$; $P = 0.03$). Endothelialitis did not correlate with antibody treatment ($N = 61$; $P = 0.78$). Patients with fibrinoid vascular necrosis did not respond to either

steroids or antibodies. Larger numbers (>4) of sampled arteries showed an improved accuracy in predicting steroid response. Fibrinoid vascular necrosis ($N = 4$; 3.6%) showed a statistically significant poor one year graft survival ($P = 0.007$). Endothelialitis (regardless of the number of affected vessels or the degree of intimal inflammation, $N = 60$; 54%), sticking of mononuclear cells to the endothelium, the extent of the interstial infiltrate (with or without eosinophils) or tubulitis did not reveal any statistically significant correlation with elevated 6 month or 1 year serum creatinine levels or one year graft survival. **Conclusion:** In ACR fibrinoid vascular necrosis has an adverse effect on one year outcome. Endothelialitis correlates with steroid resistance but is not associated with response to antibody treatment. Endothelialitis does not predict poor outcome at one year.

Islet cell transplantation in IFNγ receptor deficient mice. Are Th2 cells up-regulated? *J. Steiger, P. Nickerson, B. Ryffel, M. Hermle, D. Roubaty, M. Heim, and G. Thiel, University of Basel, Basel, Switzerland and University of Manitoba, Manitoba, Canada.* IFNγ (Th1 cytokine) is strongly associated with rejection, down-regulates Th2 cells, is responsible for DTH and the up-regulation of MHC class II. We therefore wanted to test the following hypotheses: (a) signaling through the IFNγ receptor (IFNγR) is relevant for rejection; and (b) in the absence of IFNγ signals Th2 cells would dominate the immune response. We transplanted islets from DBA/2J donors ($H\text{-}2^d$) under the renal capsule of IFNγR knock out (KO) mice ($H\text{-}2^b$) and wild type (WT) controls. Recipient mice were rendered diabetic one week prior to transplantation and graft function was determined by measuring blood glucose levels. All IFNγR KO mice rejected their islet allograft without any delay as compared to WT controls. Sequential histological examination on days 4, 6, 9 and 12 post-transplant showed a cytodestructive mononuclear cell infiltrate of the islets in both groups. To test weather rejection is mediated by T cells in IFNγR KO mice, we treated the allograft recipients with anti-CD3 (25 μg/day), which is known to delay allograft rejection by neutralizing the T cells. Under this treatment none of the treated IFNγR KO mice rejected the allograft. Intragraft cytokine gene transcripts from IFNγR KO mice and WT control were analyzed by competitive template reverse transcriptase assisted polymerase chain reaction on days 4, 6, 8 and 14 post-transplant. IL-2, IL-4, IL-10, IFNγ, granzyme B and TCRcβ gene transcripts were up-regulated after transplantation and peaked around day 8 in WT and IFNγR KO mice. Interestingly, all gene transcripts, with the notable exception of IL-4, are diminished at any given day in IFNγR KO mice compared to the WT control. Regarding the Th1/Th2 paradigm, it was striking that, although IL-4 seems to be more expressed in this IFNγ deficient system, IL-10 was decreased most markedly. We conclude that rejection in a IFNγ deficient system occurs in the same tempo as in the WT control and is mediated by T cells. Clearly, IFNγ receptor signaling is not required for allograft destruction. Although IFNγR signaling is absent and IL-4 is expressed, IL-10 gene transcripts are most markedly diminished. Therefore, polarized expression of TH2 cells was not evident. We hypothesize that rejection in these mice is mediated by an IL-2 producing Th0 like cell.

Bradykinin B2 receptor blockade interferes with renal functional development. *P. Tóth-Heyn, M. Thonney, and J.-P. Guignard, Service de Pédiatrie, Unité de Néphrologie, CHUV, Lausanne, Switzerland.* The renal kallikrein-kinin system (KKS) has been claimed to regulate morphological and functional renal maturation besides regulating neonatal glomerular hemodynamics. The present study was performed to investigate the influence of bradykinin (BK), acting via B2 receptors, on the development of renal function. Newborn rabbits were treated with the B2 receptor blocker Hoe 140 s.c. from the age of 4–5 days until the age of 8–9 days ($N = 8$). Hoe 140 was administered twice daily in a dose of 300 μg/kg. In preliminary experiments we demonstrated that this dose of Hoe 140 effectively inhibits B2 receptors for at least 6 hours in our experimental model. A control group received the same volume (0.1 ml/100 g) of 0.9% NaCl s.c. twice daily ($N = 8$). Clearance studies were performed in anesthetized newborn rabbits at the age of 8–9 days. Renal plasma flow and glomerular filtration rate (GFR) were determined by PAH and inulin clearances, respectively. Besides measuring baseline renal hemodynamics, systemic hypoxemia-induced changes were also determined in both groups. Chronic B2 receptor inhibition did not cause any difference in the kidney weights of experimental groups. Baseline blood pressure was very similar in the two groups. Renal blood flow (RBF) was higher in Hoe 140-treated newborn rabbits, but there was no difference in GFR. Control rabbits had higher filtration fraction (FF). No differences were observed in urine flow rate and sodium excretion. Systemic hypoxemia resulted in similar renal vasoconstriction in both groups. In control rabbits a decrease in GFR was observed, while in the Hoe 140 group GFR did not change, but FF increased significantly. The similar kidney weights in both groups indicate that BK does not promote neonatal renal growth. The observed difference in baseline renal hemodynamics confirms the role of BK in the functional renal maturation. Chronic B2 receptor inhibition may lead to increased RBF either by blocking the antiproliferative effect of BK or by disturbing the balance of vasoconstricting and vasodilating forces in the developing kidney. The predominant role of the vasodilating property of BK is supported by the modified vasoresponse to hypoxemia in Hoe 140 pretreated rabbits. In conclusion, intact renal KKS is necessary for the normal functional development of the neonatal kidney.

Is Neoral more nephrotoxic than Sandimmun? A prospective study. *N. Frischmuth, P. Vogelbach, H.A. Bock, and G. Thiel, Abteilung für Innere Medizin und Chirurgie, Kantonsspital Basel, Basel, Switzerland.* To evaluate whether Sandimmun (Neoral) is more nephrotoxic than "classic" Sandimmun, we prospectively studied living donor kidney recipients (excluding HLA identical siblings) who received either Sandimmun (12/88–10/94, $N = 92$) or Neoral (1/95–10/96, $N = 37$) from the time of transplantation throughout the first year. Renal function (C-inulin, C-PAH, β_2 microglobulin clearance (C-β_2m) and albumin excretion rate (AER), cyclosporine trough levels (CsA TL) and daily dose (CsA/D) were measured at 3 weeks and 1 year after transplantation. The two groups did not differ with respect to age, gender distribution, initial immunosuppressive regimen and concomitant medication (ACE inhibitors and Ca antagonists). The results are shown below.

	N	CsA/D *mg/kg*	CsA TL *μg/liter*	C-inulin *ml/min*	C-PAH *ml/min*
San 3 weeks	96	7.2 ± 0.2	249 ± 9	52 ± 2	319 ± 10
Neo 3 weeks	37	6.8 ± 0.4	295 ± 21	50 ± 3	318 ± 18
San 1 year	84	5.3 ± 1.0	156 ± 8[b]	54 ± 2	254 ± 12[b]
Neo 1 year	12	4.9 ± 0.5	194 ± 20[b]	53 ± 6	272 ± 35

	C-β_2m *ml/min*	AER *mg/24 hr*
San 3 weeks	3.7 ± 0.9	120 ± 16
Neo 3 weeks	2.2 ± 0.6	130 ± 23
San 1 year	2.1 ± 0.4	140 ± 60
Neo 1 year	1.2 ± 0.7	70 ± 28

Mean values (±SEM) for both groups. [a] $P < 0.05$; [b] $P < 0.001$ 1 year vs. 3 week values.

There was no difference between the two groups concerning CsA/D and CsA TL at 3 weeks or 1 year but there was a trend to higher CsA trough levels despite lower daily dose in the Neoral group. We found a significant decrease of C-PAH after one year in the Sandimmun but not in the Neoral group. C-β_2m as a marker of tubular toxicity and AER as a marker of glomerular toxicity tended to be lower in the Neoral group. **Conclusion:** The present data with a follow-up of one year provide no evidence of increased nephrotoxicity of Neoral compared to Sandimmun despite a higher bioavailability.

The effects of dimethyl sulfoxide used in solvent concentrations on the newborn rabbit kidney function. *M.N. Rijtema, D. Mosig, and J.-P. Guignard, Département de Pédiatrie, CHUV, Lausanne, Switzerland.* Dimethyl sulfoxide (DMSO) is a solvent, used frequently to dissolve cyclosporine, nifedipine and 8-cyclopentyl-1,3-dipropylxanthine (DPCPX). Clinically it has been used for the treatment of interstitial cystitis (RIMSO 100®) and for the treatment of scleroderma (Kemsol®).

Intravenous administration of DMSO in adult rats with doses varying between 7.4–770 μg/kg · hr has been shown to be without effect on the kidney function. The purpose of the study was to evaluate the effects of DMSO on the immature kidney. The experimental protocol included a 90 minute equilibration period, a 60 minute control period and a 90 minute lasting experimental (treatment) period. Two groups of rabbits, with ages varying between 4 and 8 days, were infused intravenously with either 111 or 16.5 μg/kg/hr of DMSO. To test for significant time-dependent trends the Page test was used followed by the Holm's correction. To test for dose-dependent effects, the deltas (value group 1–value group 2) were computed and used as data for the Page test. DMSO exhibited a dose-dependent increase in glomerular filtration rate (GFR), urine flow rate (Uf/kg), filtration fraction (FF) and renal vascular resistance (RVR) ($P < 0.001$), in combination with a dose-dependent decrease in renal blood flow (RBF) ($P < 0.001$). Furthermore, DMSO infusion resulted in a significant dose-dependent increase in the fractional excretions of sodium and chloride (FENa and FECl) ($P < 0.001$). Such low doses have previously never been found to affect renal function. Since vasoactive factors are hyperactive in the immature kidney, it was postulated that the alteration of one of these factors, probably the inhibition of prostaglandin synthesis, was responsible for the significant renal vasoconstriction. Inhibition of the already scarcely available Na^+/K^+ ATPase was postulated to be responsible for the increase in FENa and FECl. Consequently this agent should be used with caution in developmental studies.